Success of 14-day triple and quadruple therapy for the control of *Helicobacter pylori* infections in Kohat district

Syed Fahim Shah[1], Sohail Aziz Paracha[2], Waheed Ullah[3], Iqbal Muhammad[3], Somaid Iqbal[3], Aisha Gul[3], Mudassir Hussain[3], Hafiz Ullah[3], Sadir Zaman[3]

[1]Department of Medicine, Khyber Medical University, Peshawar - Pakistan
[2]Department of Anatomy, Khyber Medical University, Peshawar - Pakistan
[3]Department of Microbiology, Kohat University of Science and Technology, Kohat - Pakistan

ABSTRACT

Introduction: *Helicobacter pylori* is an important medical pathogen present in more than half of the world's population. Various treatment regimen are in use for the eradication of *H. pylori*, but due to the emergence of antibiotic resistance, its management is a big issue for clinicians.

Methods: In this study all suspected cases that had visited District Headquarters Hospital Kohat were considered for screening of *H. pylori* infections. Preliminary information about their age, gender, general health conditions, occupation, etc. was taken for consideration. After recording initial signs and symptoms, samples were considered for *H. pylori* detection using stool antigen test and endoscopy. Fourteen-day proton pump inhibitor base triple and quadruple therapy were administered to each patient.

Results: In total (n = 178), there were high numbers of positivity in patients aged below 30 years (82; 46.06%), most of whom belonged to rural areas.

Conclusion: This study concludes that there were high numbers of positive patients aged below 30 years, and according to this study MEL (Metronidazole + Esomeprazole + Levofloxacin) is the most effective treatment regimen for the eradication of *H. pylori*.

Keywords: Gastric pathology, *Helicobacter pylori*, Intestinal metaplasia, Peptic ulcer

Introduction

Helicobacter pylori is a Gram negative, microaerophilic bacteria that is very common, infecting more than half of the world's population (1). *H. pylori* infection can cause gastric inflammation, peptic ulcer, intestinal metaplasia and can lead to gastric cancer (2,3). Its urease activity, flagella mobility, adhesive proteins and S-shape help to colonize the human stomach and initiate infection (4). Besides these, the *cagA* and *vacA* genes are the major virulence factors in *H. pylori*, responsible for the gastric pathology. The *cagA* gene is responsible for peptic ulcer disease and adenocarcinoma, while the *vagA* gene causes injury to gastric epithelium

(5,6). Its invasiveness in the human stomach instigates mucosal and systemic immune responses in the infected host but it has acquired some mechanism that can evade host responses (7).

H. pylori infection rates vary by geographic location, age, ethnicity and socioeconomic status of population (8). It has been documented that infection rates are higher in poor socioeconomic conditions, particularly in developing countries (9). Its transmission takes place in different ways. Most common routes of transmission are iatrogenic, feco-oral and person-to-person contact (10,11). Along with this, contaminated food and water may be a source of infection (12).

Different strategies have been adopted for its treatment. Commonly and most acceptable treatment therapies are triple and quadruple therapy (13,14). In recent era due to the emergence of antibiotic resistance, its success has declined. Antibiotic resistance to *H. pylori* is considered the major cause of the eradication failure (15,16). One of the most enduring debates in the world is the optimal duration of therapy for its eradication (17).

The incidence of *H. pylori* eradication failure and antibiotic resistance has been documented worldwide. In Pakistan, the rate of *H. pylori* is very high due to lack of proper diagnosis of dyspepsia and the over-the-counter use of inappropriate

doses of proton pump inhibitors (PPIs). In our population of the District of Kohat, the rate of *H. pylori* infection is increasing day by day, and it is yet to find factors that lead to eruption of resistance. Therefore, keeping in view the existence data regarding its resistance and treatment failure of *H. pylori* infection, the study was conducted to determine the incidence of *H. pylori* infection and its response to different regimen of eradication in Kohat district. The aim of the study was to recognize the best treatment regimen for the eradication of *H. pylori*.

Methods

This study was conducted at the District Headquarters Hospital Kohat and Kohat University of Science and Technology, from April 2021 to December 2021. It was approved by the University Ethical Committee and written consent was taken from all patients. Only positive cases were considered in this study for further analysis.

Patients' data collection and risk factors

All the patients were asked about the issues related to gastrointestinal problems and their socioeconomic status, and all data were recorded accordingly. A questionnaire was used as the data collection tool, and it was given after obtaining written informed consent. All the patients were also questioned about their gastric information or complaints like nausea, vomiting, epigastric pain and ballottement.

Sample collection

From all suspected cases stool samples (10-20 g) were collected from all the patients and placed in a clean container. Stool antigen test was used for the detection of *H. pylori* infection. Blood sera were also collected from each patient. Three to 5 mL of blood was taken from each patient and analyzed through an automated hematology analyzer for the complete blood count (18).

Stool antigen test

Stool antigen test was performed for the detection of *H. pylori* infection. About 1 g of collected sample was diluted with the buffer present in the specimen collection tube. Suspending diluted sample for 2 min, 2-3 drops of the diluted specimen were added to the well and then waited for the appearance of faint line to read the result (19).

Treatment regimen for H. pylori eradication

Three different treatment regimen were used for control of *H. pylori* positive cases. These were **MEL** (Metronidazole + Esomeprazole + Levofloxacin), **MRL** (Metronidazole + Rabeprazole + Levofloxacin) and **MELB** (Metronidazole + Esomeprazole + Levofloxacin + Bismuth subcitrate) treatment strategies. In the designated study each patient received PPI base triple and bismuth quadruple treatment. All the patients were randomly assigned to the 14-day treatment comprising of Esomeprazole 40 mg, Rabeprazole 20 mg, Metronidazole 500 mg, Levofloxacin 500 mg and bismuth subcitrate. PPI and bismuth were recommended to be taken before meals while all the antibiotics were taken after meals. Successful eradication was defined as negative result after reconfirmation through the stool antigen test after successful 14-day therapy (20).

Statistical analysis

Qualitative and quantitative variables are shown as percentages. The relationship between hematological parameters of *H. pylori* positive patients *and H. pylori* negative control group was evaluated using confidential interval method by which the values are calculated for each parameter that will fall between intervals.

Results

In total there were 178 patients positive for *H. pylori* infection; there were 38.76% (n = 69) female and 61.23% (n = 109) male positive cases. Among the total, there were high numbers of positivity (n = 82; 46.06%) in patients aged below 30 years, while the number of positive patients in group aged 30-50 years is 38.76% (n = 69) and in that of above 50 years is 15.16% (n = 27). Of the 178 patients, 71.91% (n = 128) were living in the rural area while 28.08% (n = 50) were living in the urban area. According to the above results, high numbers of the patients were living in the rural area and only a small number of patients were living in the urban areas. The demographic information and characteristic of the suspected patients are shown in Table I.

TABLE I - Demographic characteristic of positive patients

Demographic factors	Numbers	Percentage (%)
Age		
Below 30 years	82	46.06
30-50 years	69	38.76
Above 50 years	27	15.16
Gender		
Male	109	61.23
Female	69	38.76
Literate	40	22.47
Illiterate	138	77.52
Place of living		
Rural	128	71.91
Urban	50	28.08

Gastrointestinal symptoms were almost similar in all the patients, but there were high numbers of patients who complained of epigastric pain and recurrent abdominal pain; all the patients showed more than one symptom as mentioned in Table II.

**TABLE II** - Gastrointestinal symptom of patients

Symptom	Numbers	Percentage (%)
Epigastric pain	153/178	85.95
Recurrent abdominal pain	138/178	77.52
Nausea	141/178	79.21
Vomiting	70/178	39.32
Ballottement	30/178	16.85
Water brush	65/178	36.51

The hematological parameters of *H. pylori* patients included (n = 52) *H. pylori* positive patients whose hematological values were compared with *H. pylori* negative control group (n = 52). It showed that the hemoglobin level was low in the positive patients. Comparing platelets and neutrophile, it was increased in the infected patients as shown in Table III.

TABLE III - Hematological parameter

Parameter	Patients (N = 52)	Negative control (N = 52)
Hemoglobin, g/dL	12.82 ± 1.79	14.37 ± 1.06
Platelet count, %	304,043 ± 8311.8	223,360 ± 3498
Neutrophile	61.32 ± 5.57	59.34 ± 6.91
Eosinophile	2.85 ± 0.89	3.22 ± 1.12
Monocytes	2.41 ± 0.53	4.29 ± 1.16
Lymphocytes	30.36 ± 7.80	27.87 ± 5.97

The above results show the eradication percentage of each given regimen in which 100 patients were given MEL, out of whom 88 (88%) patients showed successful eradication (Fig. 1). MRL was given to 53 patients, of whom 40 patients recovered,

Eradication percentage between MEL, MEL and MELB
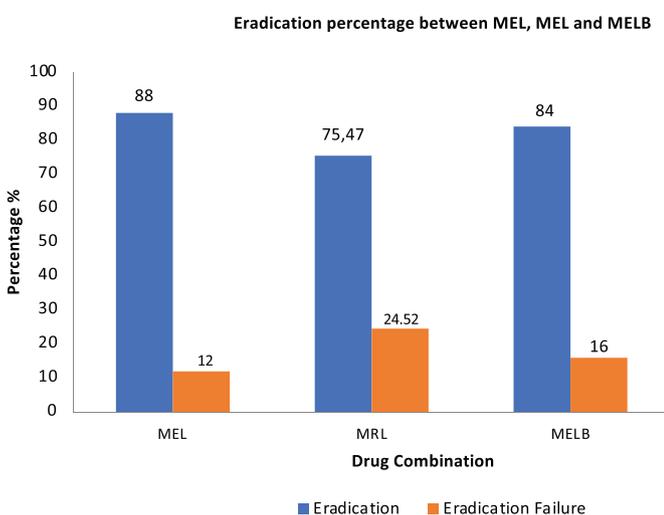
Fig. 1 - Successful eradication and failure percentage between MEL, MRL and MELB drug combinations. MEL = Metronidazole + Esomeprazole + Levofloxacin; MRL = Metronidazole + Rabeprazole + Levofloxacin; MELB = Metronidazole + Esomeprazole + Levofloxacin + Bismuth subcitrate.

exhibiting 75.47% eradication percentage. The bismuth-based quadruple therapy (MELB) was given to 25 patients, of whom 21 (84%) patients showed successful eradication after 14 days of therapy, as shown in Table IV.

TABLE IV - *Helicobacter pylori* eradication percentage between MEL, MRL and MELB regimen

Regimen	Eradication (%)	Eradication failure
MEL	88/100 (88%)	12/100 (12%)
MRL	40/53 (75.47%)	13/53 (24.52%)
MELB	21/25 (84%)	4/25 (16%)

MEL = Metronidazole + Esomeprazole + Levofloxacin; MRL = Metronidazole + Rabeprazole + Levofloxacin; MELB = Metronidazole + Esomeprazole + Levofloxacin + Bismuth subcitrate.

Discussion

H. pylori infection is the most common bacterial infection in the world, infecting about half of the world's population. This infection is more common in areas where there are poor hygienic conditions such as use of contaminated food and water. This bacterium is mainly transmitted by feco-oral route from the fecal contaminated water. The oral-oral route is also the leading cause of the infection, as few authentic studies have cultured *H. pylori* from the oral cavity (21); the oral-oral transmission has been examined in the eating of premasticated food, the use of the same spoon by mother and children (22). Various diagnostic methods have been identified for the detection of *H. pylori* but the choice usually depends on the sampling and condition of the patient. In this study, the stool antigen test has been used for the diagnosis of *H. pylori* as stool antigen test is noninvasive and rapid for the detection of *H. pylori* infection (23).

H. pylori analysis included 178 positive patients in this study in which most of the patients were less than 30 years of age. One of the studies in Egypt included 89 asymptomatic young patients, out of whom 78 were positive for *H. pylori* antigen, all aged below 30 years (24). A total of 128 patients out of 178 belonged to the rural areas, exhibiting high percentage because of the poor hygienic conditions of the people living in the rural areas. Most authentic studies have also shown that most of the *H. pylori* positive patients were from rural areas, where the environment was not hygienic. Similarly, one of the studies in Venezuela revealed that *H. pylori* in the rural population was found in 87.2% (34/39) of the patients (25). *H. pylori* is associated with a number of symptoms that are still in debate. In this study, all the patients complained of gastrointestinal symptoms, but there were high number of patients who complained about epigastric pain and recurrent abdominal pain. The main reason behind this is the hyperacidity during peptic ulcer. Primarily, gastrin and oxyntic gland are responsible for the production of more acid during *H. pylori* infection that can lead to epigastric pain (26).

In this study, we found abnormalities in some of the hematological parameters of *H. pylori* positive patients when compared to the control group. The hemoglobin level is quite lower than the control group, while the platelets and neutrophil level

TABLE V - Comparison of *Helicobacter pylori* eradication regimen (MEL, MRL and MELB)

Patient details	Treatment 1 (MEL)		Treatment 2 (MRL)		Treatment 3 (MELB)	
	Success %	Failure %	Success %	Failure%	Success %	Failure%
1. Male (n = 109)	57 (90.47%)	6 (9.53 = 2%)	17 (70.83%)	7 (30.43%)	20 (90.90%)	2 (9.09%)
2. Female (n = 69)	31 (83.78%)	6 (16.21%)	23 (79.31%)	6 (20.68%)	1 (33.3%)	2 (66.6%)
Success of treatment regimen according to age						
3. Below 30 years (n = 82)	45 (84.90%)	8 (15.09%)	12 (63.15%)	7 (36.84%)	8 (80%)	2 (20%)
4. 30-50 years (n = 69)	31 (91.17%)	3 (8.82%)	20 (83.33%)	4 (16.66%)	9 (81.81%)	2 (18.18%)
5. After 50 years (n = 27)	12 (92.30%)	1 (7.69%)	8 (80%)	2 (20%)	4 (100%)	0 (0%)
Resident wise						
6. Rural (n = 128)	60 (86.95%)	9 (13.04%)	32 (76.19%)	10 (23.80%)	14 (82.35%)	3 (17.64%)
7. Urban (n = 50)	28 (90.32%)	3 (9.67%)	8 (72.72%)	3 (27.27%)	7 (87.5%)	1 (12.5%)
Total 178	88/100 (88%)	12/100 (13.72%)	40/53 (75.47%)	13/53 (24.52%)	21/25 (84%)	4/25 (16%)

MEL = Metronidazole + Esomeprazole + Levofloxacin; MRL = Metronidazole + Rabeprazole + Levofloxacin; MELB = Metronidazole + Esomeprazole + Levofloxacin + Bismuth subcitrate

remarkably increased. This may be due to the inflammatory conditions and immune response to *H. pylori.*

Eradication of *H. pylori* needs combinations of drug treatment with adjuvant regimen that increase antibiotic activity and host responses. The duration of therapy also strongly affects the eradication of *H. pylori*. One of the studies in the United States was based on the duration of therapy of *H. pylori*, which shows that RAC (Rabeprazole, Amoxicillin, and Clarithromycin) treatment of 7 days and 10 days had a higher percentage of eradication than the 3-day treatment (27). Similarly, a study in Turkey based on levofloxacin triple therapy in which MEL was given to 92 patients showed 95.5% positive response toward MEL combination. In this study, each patient was given 14 days treatment of PPI base triple and quadruple therapy, which show that MEL had a high percentage of eradication (88/100; 88%) followed by MELB (21/25; 84%). MEL and MRL are the same triple therapy with two different PPIs (Tab. V). The reason for changing one PPI to another was that some of the patients in either group were already using that drug with the same name, so for patient satisfaction, psychologically, we changed the drug. Another reason is some of the studies showed better results with rabeprazole than esomeprazole (28).

Conclusion

This study concludes that there were high numbers of positive patients aged below 30 years in which many patients were from rural area, and according to this study MEL is the most effective treatment regimen for the eradication of *H. pylori.* This study recommends that clinicians may suggest MEL treatment for *H. pylori* positive patients for complete eradication of *H. pylori.*

Disclosures

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